Remarks and Arguments

Claims 1-15, 23 and 25-34 were rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,700,642 (Monforte '642). Claims 1-19, 23 and 25-34 were also rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,830,655 (Monforte '655). Finally, Claims 1-34 were rejected under 35 U.S.C. §103(a) as being obvious over Monforte '655 in view of U.S. Patent No. 6,251,600 ("Winger"). These rejections are identical to those of the previous office action, with most of the discussion by the examiner being repeated verbatim. The only new consideration by the examiner is with regard to the language introduced to Claim 1 in the applicants' last amendment, which specifies that the cleaving and mass spectrometric measurement of the probes occurs "one after another."

The reasons behind the aforementioned amendment are covered in detail in the applicants' last response. In a discussion accompanying that response, the applicants carefully pointed out that there are several different embodiments in Monforte '642 that are fundamentally different than each other. The following is an excerpt from the "Remarks and Arguments" section of that response:

> In an embodiment highlighted by the examiner, in which Monforte '642 uses a chip to which primers are attached, the reference discloses a "shotgun" type method of sequence analysis in which different primers are immobilized at different locations on a sample support. However, this method is limited to the situation in which there is one target sequence being sequenced. It is not used for mutation analysis of a plurality of target sequences. This is in contrast to the present invention, which uses a chip with spatially separated locations each containing a photocleavable probe for a *different* one of a number of different target sequences to be investigated. Independent Claim 1 was amended in the last response to make this distinction even more apparent, by specifying the use of "a chip with spatially separated locations each containing a photocleavable oligonucleotide probe for a different one of the target sequences to be investigated."

A first embodiment (the "shotgun" embodiment) of Monforte '642 involves different primers immobilized at different locations on a sample support, and one target sequence that is not specific to any of the primers. A description of this embodiment

may be found in the section entitled "Genomic Sequencing," which begins in column 24 of Monforte '642. The method provides a "shotgun" type sequencing technique for identifying a target sequence. As noted in the foregoing excerpt from the applicants' last response, this embodiment is limited to the situation *in which there is one target sequence being sequenced* and it is not used for mutation analysis of a plurality of target sequences.

A different embodiment of Monforte '642 was also referenced by the examiner, and this was also pointed out in the applicants' last response. This different embodiment was for the purpose of identifying pathogens or microorganisms, and is described in the section of Monforte '642 entitled "Diagnostics," and referenced in particular was column 26, lines 1-12. However, as previously noted by the applicants, "this technique is different than the shotgun sequencing technique of Monforte '642 in which primers are immobilized on a sample support." The applicants went on to state that:

> [i]ndeed, while Monforte '642 discloses the use of an immobilization surface, such as a chip, for the sequencing of one target sequence, there is no suggestion of doing so for mutation analysis of a plurality of target sequences.

Thus, this completely different embodiment (the "diagnostic" embodiment) of Monforte '642 involves one or more unique primers which are extended to provide sequence information about an adjacent segment. However, there is no suggestion that these primers might be immobilized at spatially separated locations on a chip prior to modifying all of the primers simultaneously.

Despite the applicants' arguments regarding the different embodiments of Monforte, the examiner has not acknowledged these different embodiments in the current office action. The examiner includes a brief response to the applicants' earlier arguments, but the discussion is limited. In this section, the examiner first argues that the applicants were incorrect in stating that "the Monforte method is not used for mutation analysis of a plurality of target sequences." Of course, the applicants'

argument was that the first embodiment of Monforte '642 (the "shotgun" embodiment) was not used for mutation analysis of a plurality of target sequences. In referencing the second embodiment discussed by the examiner, that of column 26, lines 1-12, the applicants' earlier response noted the following:

> As stated in this section, the objective of this technique by Monforte '642 is to identify pathogens or microorganisms. However, this technique is different than the shotgun sequencing technique of Monforte '642 in which primers are immobilized on a sample support. Indeed, while Monforte '642 discloses the use of an immobilization surface, such as a chip, for the sequencing of one target sequence, there is no suggestion of doing so for mutation analysis of a plurality of target sequences.

It is this distinction that the applicants were attempting to point out, one which the examiner's most recent remarks appear to overlook. It is therefore respectfully requested that the examiner reconsider these arguments in light of the distinction drawn by the applicants.

The examiner has also responded to the applicants' addition of the language to Claim 1 specifying that the claimed method includes cleaving and mass spectrometrically measuring the probes "one after another." The examiner argues that "both Monforte references" state that "the different sequence primers are sequentially cleaved and the presence or absence of an extension product is determined." In Monforte '642, the sentence containing this quote appears in column 24, line 64 through column 25, line 1. This sentence is part of the description of the "shotgun-type" genomic sequencing embodiment which, of course, is unrelated to the diagnostic embodiment. As discussed above, and covered in the applicants' earlier response, in the Monforte sequencing method, the primers are immobilized on a sample support. Of course, there is no such step in the mutation analysis method of Monforte '642.

Finally, in the "Response to Arguments" section, the examiner states that the applicants contend that Monforte '642 provides no teaching of an array of nucleic acids on a chip, and argues that "[t]his is simply incorrect." Column 24, lines 57-67 of Monforte '642 is cited in support of this argument. However, once again, while

paraphrasing, the examiner appears to have misunderstood the applicants' earlier arguments. Nowhere in the last amendment did the applicants state that Monforte '642 provides no teaching of an array of nucleic acids on a chip. Rather, as shown from the excerpts above, the applicants carefully drew distinctions between the different embodiments of Monforte '642, which were directed, respectively, to very different methods. There is no discussion of sequential cleaving of primers from a support surface in the embodiment of Monforte '642 that might be used for mutation analysis.

In the application of the Monforte '642 reference to the applicants claims, the examiner appears to have mixed and matched features from two very different embodiments disclosed by Monforte. The applicants took pains to distinguish between these two embodiments in their last response. However, it appears that the examiner may still be confusing the Monforte embodiments, as the citations of steps from the "shotgun sequencing" method are loosely combined with steps from the diagnostic methods. Obviously, the steps of these methods are not interchangeable, and one skilled in the art would never consider doing so when reading the Monforte '642 reference. Thus, it is respectfully requested that the examiner carefully review the specific language of the applicants' claims in light of the fact that there is no single embodiment in Monforte '642 that suggests the method as recited in Claim 1. The invention of Claim 1 is different in function and purpose than each and all of the embodiments of Monforte '642. Each of Claims 2-15, 23 and 25-34 depends ultimately from Claim 1 and is therefore equally unsuggested by the cited prior art. Reconsideration of Claims 1-15, 23 and 25-34 under this ground for rejection is respectfully requested.

Claims 1-19, 23 and 25-34 were rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,830,655 ("Monforte '655"). This rejection appears to have been repeated verbatim from the examiner's last office action, with the exception of a citation to column 38, lines 50-52 as corresponding to the new claim language added by the applicants. As mentioned in prior responses, the two Monforte patents are quite similar in subject matter, one being a continuation-in-part of the other. Indeed,

for the purposes of the broadest of the claims rejected hereunder, the application of Monforte '655 appears to parallel that of Monfore '642. Even the excerpt cited by the examiner from the Monforte '655 patent corresponds, word-for-word, to the excerpt in column 24, line 64 through column 25, line 1 of Monforte '642. As such, all of the arguments made above with regard to the allowability of Claim 1 in light of Monforte '642 are believed to apply to this rejection as well. Monforte '655 fails to suggest a method of mutation analysis of a plurality of target sequences that uses a plurality of different probes covalently bound to spatially separated locations on a chip, modifies all oligonucleotide probes on the chip synchronously to transfer information from the target sequences of the templates to the probes, and cleaves and mass spectrometrically measures the probes one after another after separating them from the templates. Each of Claims 2-19, 23 and 25-34 depends ultimately from Claim 1 and is therefore equally unsuggested by the cited prior art. Reconsideration of Claims 1-15, 23 and 25-34 under this ground for rejection is respectfully requested.

Claims 1-34 were rejected under 35 U.S.C. §103(a) as being obvious over Monforte '655 in view of U.S. Patent No. 6,251,600 ("Winger"). This rejection was also repeated from the last office action, with the exception of the citation of column 38, lines 50-52 of Monforte '655, and the references cited were discussed in the applicants' last response. Those comments are incorporated herein. In that last response, the applicants also questioned the need to apply this prior art combination to all of Claims 1-34, since most of those claims were already rejected under Monforte '655 alone.

The examiner's rejection based on Monforte '655 and Winger appears to rely exclusively on Monforte '655 as suggesting all of the limitations of independent Claim 1. However, as discussed above, there are some significant differences between this prior art reference and Claim 1 as amended. These differences persist when it is taken in combination with Winger. There is nothing in the combination of Monforte '655 and Winger that suggests a method of mutation analysis of a plurality of target sequences that uses a plurality of different probes covalently bound to spatially separated locations on a chip, modifies all oligonucleotide probes on the chip synchronously to transfer from

the target sequences of the template to the probes, and cleaves and mass spectrometrically measures the probes one after another after separating them from the templates. Each of Claims 2-34 depends ultimately from Claim 1 and is therefore equally unsuggested by the cited prior art. Reconsideration of Claims 1-34 under this ground for rejection is respectfully requested.

The applicants have made great outlays of time and money in pursuing this application through its long history of prosecution, including the allowance of the application, withdrawal from allowance, changing of examiners and need for what is now six office action responses, as well as a Request for Continued Examination. So as to advance the prosecution of the application, it is respectfully requested that a detailed analysis of the claims and the cited prior art references be provided by the examiner that takes into account the various embodiments disclosed in the Monforte references, and how each of these embodiments relate to the applicants' claims. With the examiner's assistance, the applicants look forward to moving toward a resolution of this prosecution in the near future.

In light of the foregoing amendments and remarks, it is respectfully requested that all the claims be allowed such that the application may be passed to issue. If it is believed that a telephone conference will help expedite prosecution of the application, the examiner is encouraged to call the undersigned. The Commissioner is hereby authorized to charge any additional fees due for the filing of this paper to the applicants' attorneys' Deposit Account No. 02-3038.

Respectfully submitted

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